

# Sensitive Population Subsets in Relation to Effects of Low Doses

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This paper presents an overview of current knowledge relative to identification and quantification of sensitive population subgroups, utilization of sensitive subgroups for studying low dose effects and issues in formulating environmental policies from information on sensitive subsets of the population. General factors that contribute to sensitivity are developmental periods, genetic conditions, nutritional deficiencies, predisposing diseases and personal habits. An illustration of age-related sensitivity to radiation is given, which shows that one would need to examine ten times the number of metaphase cells from individuals age 25 as from those age 55 to obtain equivalent statistical precision in identifying increased numbers of radiation induced aberrations. Hence, knowledge of susceptible subsets is useful for study design and analysis. Important concerns noted in proposing standards include: whether to protect the entire population when only a small fraction is at increased risk; what emphasis should be placed on alteration of the predisposing factors, e.g., nutrition; and how to acquire the additional protection for sensitive groups in standards based on the general population.

The problems associated with detecting in some direct fashion the effects of relatively low doses of pollutants on the health of the general population have been a topic of considerable concern during this conference. The aim of this presentation is to present a brief description of: (1) the state of knowledge relative to the identification and quantification of population subgroups that are particularly sensitive to environmental exposures of concern; (2) how current knowledge concerning sensitive subgroups can be utilized for improving upon our capability to recognize effects at low doses; and (3) the role of information derived from studies of sensitive subgroups in formulating environmental policies.

A definition of what is a "sensitive" or "susceptible" subgroup is helpful in understanding this paper. I have adopted here the definition used in bioassay studies of dose response, where sensitivity refers to the rate of change of response as the dose increases. A good synonym for sensitivity would be responsiveness to the pollutant. This definition assumes not simply that the susceptible individuals respond at lower doses, but rather that they

have steeper dose-response curves making identification of response at lower doses more feasible. This differs also from "high risk" as it is used to designate groups, for example, occupational, that experience exposures that are sufficiently high as to raise the response for the entire group exposed to levels more easily detectable.

The concern for improving our ability to identify those individuals in a population who are especially susceptible to environmental pollutants is not merely a scientific or ethical problem in setting standards for the general population, but has been mandated by law. For instance, the Clean Air Act of 1970 specified that standards would be set so as to ensure protection of susceptible, as well as healthy members of the population (1). This presupposed not only that methodology existed to define response at low levels for the general population, but also that there was a good understanding of the factors that would predispose to or accelerate disease processes in the presence of specific pollutants.

General factors that are important in delineating susceptible populations are developmental periods, genetic conditions, nutritional deficiencies, predisposing diseases and personal habits. A recent book by Calabrese (2) provides an excellent review of

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what is known about sensitive groups from a biological standpoint. Among the developmental factors he presents are immature immune and enzyme detoxification systems in fetuses and young children, circadian rhythms including phase shifts, and retention of pollutants as a function of age. He enumerates 27 genetically susceptible groups. These include albinism predisposing to ultraviolet light, inducibility of aryl hydrocarbon hydroxylase as an etiologic factor for lung cancer in the presence of polycyclic hydrocarbons, and sensitivity to respiratory irritants related to serum  $\alpha_1$ -antitrypsin. Another 12 nutritional deficiencies are implicated in sensitivity of individuals to pollutants. For example, dietary protein deficiency may lead to hypersusceptibility to DDT and other insecticides, while toxicity of ozone may be affected by vitamin E and selenium intake. Further, there seems little doubt that various chronic diseases such as kidney and liver dysfunctions and cardiorespiratory conditions are potentiated by exposure to various pollutants, even to the point of causing premature death in the chronically ill (3). Numerous studies have been carried out on susceptible groups such as bronchitics or asthmatics to ascertain their response to air pollutants (4, 5). While it is usually accepted that the chronically ill will be affected, development of appropriate epidemiologic data has not generally provided estimates useful in defining dose response or setting standards based on subgroups at risk, for reasons similar to the difficulties experienced in setting levels for the total population. In addition to the susceptibility factors mentioned above, behavioral factors, such as smoking, alcohol consumption, and drug taking, may alter the physiology of otherwise normal individuals making them more susceptible to pollutants. Thus everyone in the population will be a member of a susceptible group at certain times during life.

Careful review of available information relative to specifying various susceptible populations reveals a need for more research to document or enhance understanding of the biological mechanisms and/or to quantify the extent of the risk. It is also obvious that with increased understanding, the already extensive list of sensitive populations will continue to grow.

Knowledge of these factors is important and useful for designing studies to test environmental effects. For example, while it has been recognized that fetuses in utero, infants and pregnant women may respond to a lower level of a deleterious pollutant than at other times during the life cycle, older age also represents a sensitive time for effects that relate to deterioration of cell mediated immunity, such as cancer. In a recent paper,

Evans et al. (6) have indicated that chromosomal aberrations such as dicentric, acentric elements and rings occur more frequently at older than younger ages given the same radiation doses (Table 1). Conner (7) presented sample estimates developed by Dr. Gur and myself giving estimated number of cells required to detect increased chromosome aberrations among individuals exposed to low levels of radiation. The change in sensitivity by age makes a dramatic difference in one's ability to detect the effects of moderately low levels of radiation (Table 2). For instance, if one were to count 400 cells on each of 50 individuals at ages 25, 40 and 55, one would have a good chance of ascertaining increases associated with 1-2 rems of exposure in the oldest age or 2-3 rems of exposure in the middle age but would only pick up detectable increases at 4-6 rems in the youngest age. This is also exemplified in Table 3, which depicts the number of cells that would need to be counted to identify the minimal increases in aberrations that would be expected in association with the average exposure levels occurring during the episode at

**Table 1. Sensitivity by age to radiation induced chromosome damage.<sup>a</sup>**

| Age | Increase in aberrations/ $10^4$ /rem |
|-----|--------------------------------------|
| 25  | 1.6 $\pm$ 0.9                        |
| 40  | 3.3 $\pm$ 0.6                        |
| 55  | 5.0 $\pm$ 1.0                        |

<sup>a</sup>From Evans (6).

**Table 2. Detectable increases at selected powers in number of aberrations and corresponding dose increment for counts of 20,000 cells if background is 2.5 aberrations/ $10^4$  cells.**

| Power | No. of aberrations | Average dose by age |     |     |
|-------|--------------------|---------------------|-----|-----|
|       |                    | 25                  | 40  | 55  |
| 50    | 3.4                | 2.1                 | 1.0 | 0.7 |
| 75    | 6.5                | 4.1                 | 2.0 | 1.3 |
| 85    | 7.4                | 4.6                 | 2.2 | 1.5 |
| 95    | 9.1                | 5.7                 | 2.8 | 1.8 |

**Table 3. Sample size required (in millions of cells) for a given power to detect an increase in aberrations related to 0.1 rem dose at a 5% significance level.**

| Power | Sample size $\times 10^{-6}$ , cells |       |       |
|-------|--------------------------------------|-------|-------|
|       | 25 yr                                | 40 yr | 55 yr |
| 50    | 5.3                                  | 1.2   | 0.5   |
| 75    | 10.6                                 | 2.5   | 1.1   |
| 85    | 14.3                                 | 3.4   | 1.5   |
| 95    | 21.5                                 | 5.1   | 2.3   |

Three Mile Island. It is of interest that roughly ten times the number of cells would need to be evaluated at age 25 as at age 55 to obtain equivalent statistical precision. In this instance, even taking into account the increased susceptibility at older ages, chromosomal studies require prohibitive number of cells counted to provide reliable estimates for the low levels of radiation exposure experienced, and the decision was reached that a study was not feasible, even for the most sensitive group.

In certain situations, when feasible, a well-conducted study of the most susceptible segments of the population might be preferable to a broader study of the general population even though both have a strong likelihood of yielding "nonpositive" findings. First, if the results are nonpositive, one feels more comfortable about the remainder of the population—a result which has been achieved at lesser cost due to the smaller sample size. On the other hand, if the findings are positive, there may be a need to expand the study group to define the extent the rest of the population is at risk or to confirm the observations in other susceptible populations.

One might turn the question around, an approach which is fairly popular in practice, and attempt to identify "sensitive" subsets in studies originally designed to consider response in a general population. Such retrospective analysis is difficult methodologically and requires considerable statistical input to avoid misleading conclusions, particularly, when the overall results are nonpositive. In the positive study, one would be interested in whether the differences were consistent in all segments of the population, or whether interaction (synergism) exists between individuals with certain attributes and amount of response to the pollutant. Marked variation in subgroups can occur more frequently by chance than what would be intuitively expected. Indeed, testing sufficient subsets differences at conventional statistical significance levels ( $p < 0.05$ ) will virtually guarantee an erroneous positive finding. Even more difficult to interpret are analyses from negative investigations which consider the extremes in the responses, such as changes in pulmonary function during air pollution episodes, as representing the "sensitive" fraction of the population in the absence of *a priori* specification of subgroups of interest (8). Findings which separate the extreme responses, with no clearly distinguishable antecedent factors emerging, are difficult to visualize for use in policy setting situations and may prove difficult to validate. In spite of the reservations mentioned, when regarded as exploratory only,

appropriate analyses of subsets within larger studies may provide valuable information to distinguish potentially susceptible subgroups for further evaluation and confirmatory studies.

While recognition of the heterogeneity in human responsiveness to pollutants is important for understanding the underlying disease processes, serious problems arise in developing and implementing environmental policies which adequately take into account the multiplicity of sensitive subsets. Some important issues which arise in applying the experimental and epidemiologic evidence in formulating standards are as follows.

(1) Should one approach environmental control by protecting the entire population when only a small fraction is at increased risk? For example, certain screening tests for hypersusceptibility might make it possible to identify that proportion of an occupational group at increased risk to a work exposure. This leads to the consideration of whether it is appropriate for an employer to be permitted not to hire susceptible individuals rather than adopt more stringent controls to protect all workers.

(2) Since many of the associations between pollutants and specific subsets are still theoretical rather than firmly substantiated, how should the information be utilized in the standard setting process, recognizing that standards set on the rationale of protecting the general population do not necessarily assure adequate protection to susceptible subsets?

(3) What emphasis should be placed in environmental measures upon alterations in predisposing factors, when possible, as a means of reducing somewhat the level of risk associated with pollutant? Although additional risks associated with age, certain genetic defects, etc., may be difficult or impossible to modify, others such as general health status, nutritional factors, and behavioral traits, such as smoking and drinking, may be altered, leading to a reduction in risks.

Since identifying and protecting all susceptible groups is probably not feasible, some priority setting would seem in order that would not only take into account the evidence for the existence of a sensitive group, but also consider the number of people involved, the severity of the response, and methods for attenuating the sensitizing factor.

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